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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/018,745
Filing Date: December 21, 2001
Appellant(s): KAWAI ET AL.

Sheldon I. Landsman

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/24/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 5/24/04 has been entered as a result of an interview held on 6/15/04. It should be noted that in the advisory action mailed 6/7/04, the Examiner had stated that the amendment would not be entered. However, after reconsideration and as a result of the interview with Appellant's representative on 6/15/04, it was determined that the after final amendment would be entered.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because the summary of independent claim 21 is not consistent with that of the pending claim. In particular, independent claim 21 is directed to a pharmaceutical preparation comprising a first drug with binding affinity for plasma protein and verapamil as a second drug with binding affinity for the same plasma protein.

Appellant's summary of independent claim 14 is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Appellant's issues in regards to the 102(b) rejection of Pritchard et al is incorrect since entry of the after final amendment overcomes the rejection due to the claims being amended to encompass in vivo methods only.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 14-19 and 21-27 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Somogyi, A. "Pharmacokinetics, Bioavailability, and ECG Response of Verapamil in Patients with Liver Cirrhosis", vol12, (1981), pp. 51-60

5,977,163	Li et al	11-1999

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claim.

I. Claims 1-17, 21, 23, and 25 are rejected under 35 USC being anticipated by Somogyi et al (Br. J. Clin. Pharmac., 1981, Vol. 12, pages 51-60).

Somogyi et al disclose the pharmacokinetics, bioavailability, and ECG response of verapamil in seven patients with liver cirrhosis using stable labeled techniques wherein both an intravenous and oral dose of verapamil are administered

simultaneously (see entire document, especially, abstract). In addition, Somogyi et al disclose (1) that a stable *labeled* (14C-verapamil) oral solution of verapamil is administered simultaneous with and *unlabeled* intravenous dose of the drug (page 51, column 2, first complete paragraph; page 52, columns 1 and 2, bridging paragraph; page 52, column 2, 'Plasma protein binding and erythrocyte distribution'; page 55, Figure 1 and 2). (2) Antipyrine was administered to patients as an oral solution. Likewise, indocyanine green was administered as a bolus dose (page 52, column 2, first complete paragraph). Furthermore, Somogyi et al disclose that most of the patients in their study were receiving cimetidine and/or spironolactone. The co-administration of cimetidine and/or spironolactone with verapamil may have affected the bioavailability and oral clearance of verapamil (page 59, column 2, first complete paragraph).

In addition, on page 52, columns 1-2, bridging paragraph, it is disclosed that verapamil was administered both by intravenous and oral route simultaneous using stable labeled techniques. An intravenous (unlabeled) dose of verapamil in HCl and saline was administered in combination with an oral dose of d_3-verapamil (trideuterated verapamil at the methoxy group of the benzene ring para to the quaternary carbon atom).

Thus, both Somogyi et al and Appellant disclose a pharmaceutical composition wherein a first drug (cimetidine and/or spironolactone) is administered prior to the administration of verapamil. Also, Somogyi et al disclose the simultaneous administration of different forms of verapamil (labeled and unlabeled) to a subject.

Note: It is duly noted that Appellant's independent claims do not specify that the various derivatives of a drug may not be administered as the first and second drugs. Also, it should be noted that Somogyi et al disclose that most of the patients in their study were receiving cimetidine and/or spironolactone and that the co-administration of those drugs with verapamil may have affected the bioavailability and oral clearance of verapamil.

II. Claims 14, 16-19, and 21-27 are rejected under 35 USC 103(a) as being unpatentable over Somogyi et al (Br. J. Clin. Pharmacol., 1981, vol. 12, pages 51-60) in view of Li et al (US Patent No. 5,977,163).

Somogyi et al (see discussion above) fail to disclose a kit comprising the first and second drug and other possible radiolabels and/or chelators that may be used to radiolabel drugs.

Li et al disclose water-soluble prodrugs (see entire document, especially, abstract). The methods disclosed by Li et al may be used to generate a water-soluble polymer conjugate of other therapeutic drugs that include verapamil (column 2, lines 56-68). The complexes may be radiolabeled with various metals (columns 3-4, bridging paragraph). Likewise, the complexes may be conjugated to various chelators including DTPA, DOTA, TETA, SMSA, DTTP, HEDP, and DPDP to name a few (column 4, lines 4-17). The complexes of Li et al may be imaged using single photoemission computer topography or positron emission tomography (column 8, lines 34-47) or another method

depending upon the nuclide selected (columns 3-4, bridging paragraph; column 8, lines 52-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Somogyi et al using the teachings of Li et al and generate a kit comprising the first and second drug and attach various radiolabels and/or a chelator to the drug composition because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate. The conjugates may be radiolabeled with aluminum, boron, calcium, copper, gadolinium, gallium, indium, iron, rhenium, samarium, technetium, thallium, yttrium, zinc, and tin to name a few metals. Likewise, it would have been obvious to incorporate a chelator since Li et al disclose that possible chelators, include but are not limited to, DTPA, DOTA, TETA, SMSA, DTTP, HEDP, and DPDP to name a few. Also, it should be noted that it would be obvious to a skilled practitioner to label the complex with carbon-11 since both carbon-14 and carbon-11 are radioisotopes of carbon and Li et al disclose that the subject may be imaged using single photon emission computer tomography or positron emission tomography. Furthermore, it is noted that since both Somogyi et al and Li et al disclose the use of verapamil in combination with another drug that may be radiolabeled, the references may be considered to be within the same field of endeavor. Hence, the references are combinable.

(11) Response to Argument

I. Appellant's assertions in regards to the 102(b) rejection may be summarized as (a) Somogyi et al does not disclose the administering of verapamil as a second drug that regulates the binding of a first drug to the plasma protein. (b) Even though Somogyi et al disclose that antipyrine and indocyanine green were administered as a bolus dose to a patient that was being treated with verapamil, there is no discussion of protein binding. (c) While the cited prior art discloses at page 59 that most of the patients being treated with verapamil were receiving cimetidine and/or spironolactone, and that the co-administration of these drugs with verapamil may have affected the bioavailability and oral clearance of verapamil, the disclosure does not state that bioavailability and clearance were, in fact, affected, but only speculates that they may have been affected. (d) While Somogyi et al discuss the binding to plasma protein at various places in the document, none of the disclosures specifically state that the second drug regulates the binding of the first drug to the plasma protein.

The following arguments are made with regard to the assertions above. Somogyi et al disclose the administering of verapamil as a second drug. For example, see page 52, columns 1-2, bridging paragraph, wherein and unlabeled solution of verapamil is administered in combination with a trideuterated form of verapamil. In addition, plasma protein binding of verapamil was analyzed (see pages 52-53, bridging paragraph). Also, it should be noted that it would be inherent that if you have two forms of the same drug that desire the same binding site wherein the drugs are co-administered, then there will be a competing for the binding site. Furthermore, Somogyi et al discloses

various instances wherein verapamil is administered in combination with another drug. Also, it is noted that while Appellant acknowledges that Somogyi et al discloses the binding to plasma protein at various places in the document, since the document does not specifically state that the second drug regulates the binding of the first drug to the plasma protein, the prior art does not read on the instant invention. Appellant is reminded that a reference must be considered for what it teaches as a whole. Specifically, as previously stated, it is recognized in the art that when there are two drugs present that bind to the same site, co-administering the drugs results in the drugs competing for the same site.

II. Appellant's assertions in regards to the 103(a) rejection may be summarized as (a) Li et al does not disclose verapamil in combination with another drug that may be radiolabeled. (b) Li et al does not supply the deficiencies of Somogyi et al and thus, do not disclose or suggest the in vivo administering of a second drug that regulates binding of the first drug.

First, for clarification of the record, the Examiner stated that the methods disclosed by Li et al may be used to generate a water-soluble polymer conjugate of other therapeutic drugs which include verapamil (column 2, lines 56-68). This statement should be interpreted as Li et al disclosed verapamil as a therapeutic drug, not as verapamil in combination with another drug. Furthermore, as set forth previously, the secondary reference, Li et al, disclosed kits comprising various chelators and radiolabels which may be conjugated to therapeutic drugs which listed verapamil as a

possible drug. Thus, the references were combined on that basis. Also, it is noted that Li et al disclose in column 2, lines 56-68, that the polymer conjugates of other therapeutic agents which include verapamil is well within the skill of a routine practitioner in the chemical arts and would fall within the scope of their invention. Li et al further disclose that in column 3, lines 5-8 that the conjugates may be administered in conjunction with other drugs and that such combinations are known in the art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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